UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/783,259	02/20/2004	Kenichiro Hasumi	358690-00005-1	7322

7590 04/09/2007

Debra Z. Anderson
Eckert Seamans Cherin & Mellott, LLC
44th Floor
600 Grant Street
Pittsburgh, PA 15219

EXAMINER	
HUMPHREY, LOUISE WANG ZHIYING	
ART UNIT	PAPER NUMBER
1648	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/09/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/783,259	HASUMI ET AL.	
	Examiner	Art Unit	
	Louise Humphrey, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 January 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-15* is/are pending in the application.

4a) Of the above claim(s) *3-5,7,8 and 12-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6 and 9-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Response to Arguments

This Office Action is in response to the amendment filed 12 January 2007. Claim 2 has been cancelled. Claims 1 and 3-15 are pending. Claims 3-5, 7, 8 and 12-15 are withdrawn. Claims 1, 6 and 9-11 are under final rejection.

Claim Rejections - 35 U.S.C. §112

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 1 and 6, under 35 U.S.C. §112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims, is **withdrawn**. Applicant's arguments and the Mann Declaration under 37 CFR 1.132 filed on 12 January 2007 are not persuasive. However, a review of the prior art shows sufficient support for the preparation of LCM derived from naïve T cells by activation with anti-CD3 and anti-CD28-coated beads (see rejection under 35 U.S.C. §103 below).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims 1 and 9-11, under 35 U.S.C. §103(a) as being obvious over Baxevanis *et al.* (1997) in view of Setaluri *et al.* (US 2002/0192727), is **withdrawn** in view of the amendment adding the limitation of lymphocyte conditioned media derived from naïve T cells cultured with antiCD3- and antiCD28-coated beads.

The rejection of claims 1 and 9-11, under 35 U.S.C. §103(a), as being obvious over Baxevanis *et al.* (1997) in view of Setaluri *et al.* (US 2002/0192727) and Mengozzi *et al.* (2001) is **maintained**.

The amended claims are directed to a method of enhancing an immune response to an antigen in a mammal comprising administering lymphocyte conditioned media (LCM) derived from naïve T cells cultured with antiCD3- and antiCD28-coated beads in combination with a vaccine of said antigen to said mammal.

Examiner's rejection in the Action mailed on 08 August 2006 is as follows:

Baxevanis *et al.* describe a method of adding supernatants collected from donor-derived PBMC, which contains naïve T cells, stimulated with anti-CD3 monoclonal antibody.

Baxevanis *et al.* do not describe anti-CD3/CD28-coated beads for T cell activation and are silent on the antigen to be administered with the activated PBMC supernatant.

Setaluri *et al.* describe the dosage calculation and the administration of a tumor antigen hourly, daily, weekly, monthly, or yearly, by intramuscular or intravenous injection. See column 10, ¶90 and 92.

Mengozzi *et al.* suggest that anti-CD3/CD28-coated beads can be utilized for *ex vivo* stimulation of T cells.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Baxevanis *et al.* by activation with anti-CD3/CD28-coated beads, as taught by Mengozzi *et al.*, and by combining with a tumor antigen and adapting the dosage calculation, administration route and schedule taught

by Setaluri *et al.* The skilled artisan would have been motivated to do so to increase the efficiency of activation of T cell and the immunogenicity of the tumor antigen, by enhancing NK cell-mediated cytotoxicity, and activating the up-regulation of IL-2-specific receptor, cytokine synthesis and secretion, cell proliferation and acquisition of both antigen-specific and antigen-non-specific T-lymphocyte cytotoxicity. There would have been a reasonable expectation of success, given the *ex vivo* expansion of even HIV-infected T cells after anti-CD3/CD28 stimulation, as taught by Mengozzi *et al.* and the standard pharmaceutical procedures for administration of an anti-tumor antigen, as taught by Setaluri *et al.* Thus, the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Applicants argue the following: (1) the prior art does not make the modification obvious unless the prior art suggests the desirability of the modification; (2) Baxevanis *et al.* do not teach or suggest coating anti-CD3 onto beads; (3) the disclosure of Setaluri *et al.* relates specifically to MAP-2 expression and the administration of a tumor antigen, which is not relevant as claim 1 is not directed to the administration of a cancer antigen.

Applicant's arguments have been fully considered but are not persuasive. The motivation and suggest for making the modification is present in the cited prior art, as set forth the previous Action, which has been repeated above. Mengozzi *et al.* describe naïve T cells cultured with anti-CD3- and anti-CD28-coated beads. See first sentence in abstract. The suggestion is expressly disclosed in Mengozzi *et al.*, who describe that CD3/CD28 stimulation (i.e., antibodies co-immobilized on beads), one of the most powerful stimulants of cell activation and proliferation, results in maximal replication of naïve T cells. See page 11648, left column, last four lines, and right column, first full paragraph. This disclosure cures the deficiency in the disclosure by Baxevanis *et al.*

In response to Applicants' allegation of the irrelevance of Setaluri *et al.*, Examiner advises Applicants to argue according to the claim language. The language of claim 1 recites "an antigen," which does not exclude a cancer or tumor antigen. Therefore, the disclosure of Setaluri *et al.* clearly meets the claim limitations when combined with Baxevanis *et al.* and Mengozzi *et al.* as a whole.

New Claim Rejection Necessitated by Amendment - 35 USC § 103

Claims 1 and 6 are rejected under 35 U.S.C. §103(a) as being unpatentable over Baxevanis *et al.* (1997) in view of Meidenbauer *et al.* (2000) and Mengozzi *et al.* (2001).

The instant claims are drawn to a method of enhancing an immune response to an antigen in a mammal comprising administering lymphocyte conditioned media (LCM) derived from naïve T cells cultured with antiCD3- and antiCD28-coated beads in combination with a vaccine of said antigen to said mammal. The antigen is limited to a prostate-specific antigen (PSA) in claim 6.

Meidenbauer *et al.* disclose administering a PSA-based vaccine in combination with granulocyte-macrophage colony-stimulating factor, which induces cellular immune response to human PSA predominantly mediated by T lymphocytes. See Abstract. The method involves administration of the PSA-based vaccine in combination with light mineral oil as an adjuvant. Meidenbauer *et al.* further disclose *in vitro* induction of PSA-reactive lymphocytes by stimulating PBMC with pulsed dendritic cells. See page 91, *In Vitro* Sensitization. Meidenbauer *et al.* do not disclose administering LCM derived from naïve T cells cultured with antiCD3- and antiCD28-coated beads.

Baxevanis *et al.* describe a method of induction of tumor-antigen-specific lymphocytes, which is an immune response, by adding supernatants collected from peripheral blood mononuclear cells (PBMC), containing naïve T cells, derived from cancer patients and stimulated with anti-CD3 monoclonal antibody immobilized on tissue culture flasks. See page 1072, right column, and page 1075, left column, Preparation of ACD3S. Baxevanis *et al.* do not describe anti-CD3 and anti-CD28-coated beads.

Mengozzi *et al.* suggest the method of stimulation of naïve T cells with anti-CD3/CD28-coated beads. See page 11648, Discussion.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Meidenbauer *et al.* by combining a cancer antigen like PSA with the supernatant of stimulated cancer patient-derived PBMC containing naïve T cells as taught by Baxevanis *et al.* and by replacing immobilized anti-CD3 antibodies with anti-CD3 and anti-CD28-coated beads for stimulation of naïve T cells, as taught by Mengozzi *et al.* The skilled artisan would have been motivated to do so to increase the efficiency of activation of T cell and the immunogenicity of the cancer antigen, by enhancing NK cell-mediated cytotoxicity, and activating the up-regulation of IL-2-specific receptor, cytokine synthesis and secretion, cell proliferation and acquisition of both antigen-specific and antigen-non-specific T-lymphocyte cytotoxicity, as suggested by Baxevanis *et al.* on page 1072, right column. There would have been a reasonable expectation of success, given that supernatants harvested from PBMC cultures stimulated with soluble anti-CD3 have been demonstrated to induce autologous

lymphocytes *ex vivo* to display durable anti-tumor cytotoxic responses in clinical trials (Baxevanis *et al.*, page 1072, right column, last four lines), and the significant proliferation of naïve T cells after anti-CD3 and anti-CD28 stimulation, as taught by Mengozzi *et al.* Thus, the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Applicant's amendment necessitated the new ground of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Contact Information

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louise Humphrey, Ph.D. whose telephone number is 571-272-5543. The examiner can normally be reached on Mon-Fri, 9:30 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell, can be reached at 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Jeffrey Parkin, Ph.D.
Primary Examiner
30 March 2007

Louise Humphrey, Ph.D.
Assistant Examiner